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Case HP/5-21551/A

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF ANDREAS WERNER SUPERSAXO ET AL

Group Art Unit: 1619

SERIAL NO.: 09/306,006

Examiner: S. SHARAREH

FILED: JUNE 5, 1999
FOR: USE OF NANODISPERSIONS IN PHARMACEUTICAL END FORMULATIONS

Assistant Commissioner for Patents
Washington, D.C. 20231

DECLARATION UNDER RULE 132

I, Andreas Werner Supersaxo, a citizen of the Swiss Confederation, residing in Baar, Switzerland, hereby declare:

1. That I am a co-inventor of the invention disclosed and claimed in the above identified patent application;

2. That I have been employed by Vesifact AG since January 1, 1998. specializing in research of nano-sized carrier systems for life science products;

3. That I am presently head of R & D, and have held this position since January 1, 1998;

4. That I am engaged in the research and development of nano-sized carrier systems for life science products;

5. That I consider myself an Expert in preparation of drug delivery systems, especially lipid based delivery systems such as liposomes, mixed micelles and microemulsions;

6. That prior to my employment at Vesifact AG, I was an employee of F. Hoffmann-La Roche AG Basel, Switzerland and of Syntex Research, Palo Alto, California, USA;

7. That I received my Ph. D. in pharmaceutics in 1986 at the Swiss Federal Institute of Technology, Department of Physical Pharmacy, Zurich, Switzerland;

8. That I am a named inventor in U.S. Patents Nos.: 5,376,646; 5,416,202; 5,470,582; 5,759,827 and 6,030,602.

9. That I carried out the following preparative Examples (1A), (1B), (2A) and (2B):

1. Composition of formulations

1.1. Formulation 1A (Example 4 of US 6,245,349) and 1B (modified Example 4 of US 6,245,349)

The formulations 1A and 1B were prepared according to Example 4 of US 6,245,349.

Miglyol 812, Lipoid S100, Tween 80 and Propylene Glycol (1A) or Ethanol (1B) was mixed together to an initial solution. The Hydrocortisone was then added with stirring by means of a magnetic stir bar until the drug was completely dissolved as determined by visual inspection. The obtained solution was then diluted with the phosphate buffer to produce the final formulation. Finally, the formulation was filtered through a 0.22 micron filter.

Components	Concentration (% w/w)	
	1A (Prior Art)	1B (Comparison)
Hydrocortisone	0.10	0.10
Migylol 812 (corresponds to Captex 300)	4.20	4.20
Lipoid S 100 (corresponds to Phospholipon 90 G)	1.30	1.30
Tween 80	2.90	2.90
Propylene Glycol	1.50	0.00
Ethanol	0.00	1.50
10 mM Phosphate Buffer, pH 7.4	90.00	90.00

1.2. Formulation 2A (Example 16 of the present US application) and 2B (modified Example 16)

The formulations 2A and 2B were prepared according to Example 16 of the present application.

Vitamin A Palmitate, Miglyol 812, Lipoid S100, Tween 80 and Ethanol (2A) or Propylene Glycol (2B) was mixed together to an initial solution. The obtained solution was then added with stirring by means of a magnetic stir bar to the phosphate buffer at 50°C to produce the final formulation. Finally, the formulation was filtered through a 0.22 micron filter.

Component	Concentration (% w/w)	
	2A (Example 16)	2B (Comparison)
Vitamin A Palmitate (1.7×10^6 IU/g)	0.45	0.45
Migylol 812 (corresponds to Captex 300)	3.00	3.00
Lipoid S 100 (corresponds to Phospholipon 90 G)	1.73	1.73
Tween 80	3.40	3.40
Ethanol	1.42	0.00
Propylene Glycol	0.00	1.42
10 mM Phosphate Buffer, pH 6.0	90.00	90.00

2. Particle Size Analysis

The particle size and particle size distribution of the obtained formulations w r determined by dynamic laser light scattering using the Nicomp 380 Submicron Particle Sizer. The data reported in Table 1 correspond to the Number Weighted Gaussian Analysis.

3. Results and Conclusions

Table 1. Particle size and particle size distribution of formulation 1A, 1B, 2A and 2B

Formulation	Mean Diameter [nm]	Standard Deviation [%]
1A -PA	9.5	53.5
1B His	39.3	49.9
2A His	12.9	30.6
2B - PA	5.7	70.5

4. I, Andreas Werner Supersaxo, further declare that the data presented in Table 1 show that the Hydrocortisone formulation (Example 4, US Patent No 6,245,349) and the Vitamin A Palmitate formulation (Example 16, present application) can be prepared with both, propylene glycol and ethanol. The particle size of the Ethanol based formulations is somewhat larger compared to the Propylene Glycol based ones. However, using Ethanol instead of Propylene Glycol results, especially in the case of the Vitamin A Palmitate formulation in significantly more homogeneous formulations. The homogeneity of the Vitamin A Palmitate formulation is comparable to the one of the Nanosphere™ Size Standard, Nominal 20 nm, Duke Scientific Corporation, Palo Alto, CA 94303. This is an important advantage since a homogeneous formulation is a prerequisite to get a reproducible drug distribution and hence drug effect.

This behavior could not be expected from a person having ordinary skill in the art.

5. I, Andreas Werner Supersaxo, further declare that all statements made herein of personal knowledge are true and all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed this 17th day of December 2002

Andreas W. Supersaxo

Andreas Werner Supersaxo